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Pulmonary and Percutaneous Absorption of 2-Propoxyethyl Acetate and 2-Ethoxyethyl Acetate in Beagle Dogs

by Derek Guest,*† Marva L. Hamilton,* Peter J. Deisinger* and George D. DiVincenzo*

A comparison was made of the absorption and elimination rates of 2-propoxyethyl acetate (PEA) and 2-ethoxyethyl acetate (EEA) following inhalation, dermal application or IV administration. Male beagle dogs were exposed to 50 ppm PEA or EEA for 5 hr, and breath samples were collected during the exposure and a 3-hr recovery period. Both compounds were rapidly absorbed through the lungs. After 10 min of exposure, the concentrations of the parent compounds in the expired breath were 5 to 10 ppm (80–90% absorption) and reached plateau values at about 3 hr of 13 ppm for PEA (74% absorption) and 16 ppm for EEA (68% absorption). Post-exposure breath samples declined exponentially to 0.5 ppm and 2 ppm after 3 hr for PEA and EEA, respectively. Expired concentrations of PEA were slightly, but significantly ($p < 0.025$), lower than those of EEA at corresponding times during the exposure. After IV dosing with 1 mg/kg [ethyl-1,2-^{14}C]PEA, the urine contained 61% and 88% of the dose in 4 and 24 hr, respectively. [^{14}C]EEA was eliminated more slowly, with 20% and 61% of the dose appearing in the urine in 4 and 24 hr, respectively. Blood elimination half-lives were 1.6 hr for [^{14}C]PEA and 7.9 hr for [^{14}C]EEA. Only trace amounts of $^{14}CO_2$ (< 1%) or volatile materials (< 0.1%) were detected in the expired air with either compound. For studies of percutaneous absorption, [^{14}C]PEA or [^{14}C]EEA was added to undiluted compound and applied in a glass cell to a shaved area on a dog's thorax for 30 or 60 min. Blood and expired air were collected for 8 hr and urine for 24 hr. The pattern of urinary elimination for each compound was similar to that seen after IV dosing, with [^{14}C]PEA being excreted more rapidly than [^{14}C]EEA. Although the excretion rates for the two compounds were markedly different, the absorption rates were similar. Estimated over a 60-min period, the percutaneous absorption rates were 116 and 110 nmole/cm^2/min for PEA and EEA, respectively. These values are similar to those for other lipid-soluble compounds. Taken together, these data may be extrapolated to allow the estimation of PEA and EEA uptake in man.

Introduction

The ethylene glycol ethers have been used extensively in industry and consumer products for a number of years. They are highly miscible with water and organic solvents and have found application in coatings, dyes, insecticides, soaps and cosmetics. Exposure may therefore occur both by skin contact and inhalation.

In general, this class of compounds exhibits low to moderate toxicity and only slight skin irritation, even though most are readily absorbed percutaneously (*1*). Recent reports, however, have indicated that some ethylene glycol ethers and their acetic acid esters produce reproductive effects in laboratory animals (*2–5*). Both 2-ethoxyethanol and 2-ethoxyethyl acetate have been reported to produce teratogenic effects and testicular changes in rodents (*2,5,6*). After repeated, high oral doses (2200–4400 mg/kg), 2-propoxyethyl acetate produced testicular atrophy in rats (*7*). 2-Propoxyethanol administered orally for 6 weeks at approximately 1500 mg/kg did not produce reproductive effects in male rats (*2*).

In view of these findings, a comparison was made of the absorption and elimination rates of two glycol ether derivatives, 2-propoxyethyl acetate and 2-ethoxyethyl acetate, in dogs after inhalation, dermal application or intravenous administration.

Materials and Methods

Materials

[Ethyl-1,2-^{14}C]2-propoxyethyl acetate ([^{14}C]PEA) and [ethyl-1,2-^{14}C]2-ethoxyethyl acetate ([^{14}C]EEA) were purchased from California Bionuclear Corporation (Sun Valley, CA). The radiochemical purity of each compound was determined by gas chromatography and radiochemical detection with a Gas Proportional Counter (Model

*Biochemistry Section, Health, Safety, and Human Factors Laboratory, Eastman Kodak Company, Rochester, NY 14650.
†Author to whom all correspondence should be addressed.

894, Packard Instrument Co., Downers Grove, IL). Both isotopic materials were found to be greater than 98% radiochemically pure, each with a single radioactive contaminant, probably the corresponding alcohol. The specific radioactivity of the [^{14}C]PEA was 40.0 μCi/mg and that of the [^{14}C]EEA was 17.4 μCi/mg.

Nonradioactive PEA (Eastman Chemical Products, Kingsport, TN) and EEA (Kodak Laboratory Chemicals, Rochester, NY) were assayed for purity by GC–MS; PEA was greater than 98% pure and EEA was 95% pure (major impurity ethylene diacetate).

Animals

Male beagle dogs weighing 10 to 13 kg were obtained from Marshall Research Animals, Inc. (North Rose, NY). Dogs used for skin application and intravenous (IV) administration experiments were fasted for 16 hr before use. A suitable area of skin on the dog's thorax was shaved one day prior to a skin absorption experiment. Atropine sulfate and Ace-Promazine were administered as pre-anesthetics. Dogs were anesthetized with sodium pentobarbital for the duration of the experiment. Dogs used for inhalation experiments were not fasted prior to use.

Methods

Inhalation Exposure. Inhalation exposures were conducted at a concentration of 50 ppm with either PEA (299 mg/m^3) or EEA (270 mg/m^3). Two animals, housed in separate cages, were exposed in each experiment. Four animals were exposed to each compound.

The exposure facility consisted of a 32,000 L interior room, equipped with an independent, adjustable air supply system. The exposure room was maintained at a slight negative pressure. Filtered air was supplied to the exposure facility at a rate of 10,000 L/min which resulted in 19 air changes per hour.

The test substance was metered into a 5-L round-bottomed flask by using a dual syringe pump (Modern Metalcraft, Midland, MI). The flask was heated to 110°C, and the vaporized compound was flushed from the flask with a stream of dried nitrogen (50 L/min). The vapor was carried into the room air supply via 1/2 in. stainless steel tubing. The room concentration of test compound was monitored continuously with a Beckman Model 400 Hydrocarbon Analyzer (Beckman Instruments, Inc., Fullerton, CA). The hydrocarbon analyzer was calibrated with a 50 ppm standard of each test compound. The time-weighted average exposure concentrations, calculated from the output of the hydrocarbon analyzer, were 50.3 ± 1.6 ppm for PEA and 50.8 ± 1.1 ppm for EEA ($\bar{x}$ ± SD). A sample of room air was collected during each exposure and assayed by gas chromatography to verify the room concentrations.

All sample handling systems used in these experiments were fabricated of either Teflon, glass or stainless steel. Expired air samples were collected utilizing a close-fitting mask fabricated from Teflon. The mask was constructed with a sampling port connected to a length of Teflon tubing, a breathing port, and a pressure indicator. At sampling times, the mask was strapped to the animal's head, and a 25-mL repeating dispenser (Brinkmann Instruments, Westbury, NY) was connected to the sampling port of the mask. A 750-mL Teflon gas sampling bag was connected to the outlet of the repeating dispenser. A breath sample was aspirated from the mask on the upstroke of the dispenser and dispensed into the gas sampling bag on the downstroke. Pooled end tidal breath samples (approximately 30 breaths) were collected during the late phase of exhalation.

A breath sample was collected from each dog before it entered the inhalation chamber and after 10, 20, 40, 60, 90, 120, 180, 240 and 300 min of exposure. The dogs were removed from the chamber and breath samples were collected at 10, 20, 40, 60, 90, 120 and 180 min after exposure.

Breath and room atmosphere samples were analyzed on a Varian 2100 gas chromatograph (Varian Instrument Division, Palo Alto, CA) equipped with a flame ionization detector. Gaseous samples were injected through a 25-mL sampling valve (Carle Instruments, Inc.). Gas chromatographic separation was achieved on a 6-ft glass column packed with 20% Carbowax 20M on 80/100 Gas-Chrom Q at 75°C. For quantitation, sample peak areas were compared to those of external standards. The standards were prepared by vaporizing a measured volume of test compound with air metered through a Singer No. 802 Flowmeter (Singer, American Meter Division) into a Teflon gas sampling bag.

Statistical evaluation of the data was accomplished with a program developed by the Statistical Analysis System Institute (*8*).

Intravenous Administration. For intravenous administration experiments, the radioactive compound was added to a solution of the nonradioactive compound in saline to give a final concentration of 5 to 10 mg/mL. Approximately 3 mL of this solution (containing about 10 μCi) was administered via an in-dwelling forelimb intravenous catheter at a dose level of 1 mg/kg body weight.

Expired air was collected continuously into a Teflon bag by means of an endotracheal tube connected to a two-way valve and passed through silica gel and sodium hydroxide traps to absorb expired volatile organic materials and carbon dioxide, respectively.

Blood samples were collected in heparinized tubes at intervals up to 8 hr. A continuous saline drip was maintained throughout the experiment to replace lost body fluids. Urine samples were collected at 4 and 8 hr by means of a urethral catheter. Overnight urines (8–24 hr) were collected from conscious dogs housed after recovery in stainless steel metabolism cages.

A Packard Tri-Carb scintillation spectrometer (Model 2660, Packard Instruments, Downers Grove, IL) was

used for the determination of radioactivity. Radioactive samples were dissolved in Eastman Ready-to-Use II scintillation fluid (Eastman Kodak Company, Rochester, NY). A Packard sample oxidizer (Model 306) was used for the measurement of radioactivity in blood samples.

Skin Exposure. For dermal application an appropriate quantity of radioactively labeled compound was added to 25 mL of undiluted nonlabeled compound and a portion (40 μCi, 15 mL) was transferred to a sealed, glass absorption cell secured to the dog's thorax with surgical tape and adhesive (Skin Bond, Howmedica Inc., Largo, FL). Cotton gauze inside the cell facilitated a uniform distribution of the solution. The absorption cell measured 15 cm long, 3 to 4 cm wide and 1.5 cm deep with a skin contact surface area of 55.6 cm^2. Exposures were carried out for 30 or 60 minutes.

Expired air, blood and urine samples were collected and analyzed as described above. Absorption rates were calculated after correction for incomplete excretion of material using the data obtained from IV experiments.

In Vitro Percutaneous Absorption

Whole skin was removed from the thorax of beagle dogs at necropsy, and kept moist with saline under refrigeration until used. Subcutaneous fat was removed and sections (approximately 1.5 cm diameter) cut to fit across a glass diffusion cell (Franz diffusion cell, Crown Glass Co., Somerville, NJ). The skin contact area was 0.9 cm^2. The lower chamber of the cell was filled with isotonic saline maintained at 37°C. The absorption rates of [^{14}C]PEA and [^{14}C]EEA were determined by placing an excess of compound (0.3 mL, 1.5 μCi) in the upper chamber of the cell and measuring its appearance in the lower chamber hourly from 2 to 7 hr.

The values obtained at each time point were corrected for loss of material due to sampling. Six to eight cells were run for each compound using skin from each of two dogs. The absorption rates were calculated by linear regression analysis of the data from the time that steady state absorption was obtained.

An estimate of the integrity of the skin sample in each cell before and after exposure to [^{14}C]PEA or [^{14}C]EEA was obtained by determination of the permeability of the preparation to tritiated water. These measurements also provided an indication of the potential of each compound to cause irreversible skin damage that would lead to an increase in permeability. The damage ratio was calculated as the ratio of the tritiated water permeability after skin contact with the glycol ether to the initial tritiated water permeability.

Results

Inhalation Exposures

Analysis of the end tidal air samples during exposure to 50 ppm of PEA or EEA indicated that both compounds were rapidly absorbed through the lungs. The breath concentrations of PEA and EEA showed a rapid increase with the duration of exposure and reached a plateau after about 3 hr. After 10 min of exposure to PEA, 5 ppm PEA was detected in the end tidal air, indicating that 90% of the inhaled vapor was absorbed. PEA concentrations in breath reached a plateau at about 13 ppm which indicated that 74% of the inhaled PEA was absorbed. After 10 min exposure to EEA, 9 ppm EEA was detected in the breath (ca. 80% absorption). The EEA concentration reached a plateau at about 16 ppm, indicating that 68% of the inhaled compound was absorbed.

Post-exposure breath samples showed a rapid, exponential decline for both compounds. At 10 min, the PEA breath concentration was 5 ppm and declined to 0.5 ppm at 3 hr post-exposure. The breath concentration of EEA was 7 ppm at 10 min and decreased to 2 ppm at 3 hr post-exposure.

The serial expired air PEA concentrations were consistently lower than the EEA concentrations at corresponding times during and after the exposure (Fig. 1). These findings were statistically significant ($p < 0.025$) during the exposure. Linear regression analysis of the curves during the exposures showed no significant differences in the slopes, indicating that there was a similar rate of equilibration in the lungs for these two compounds.

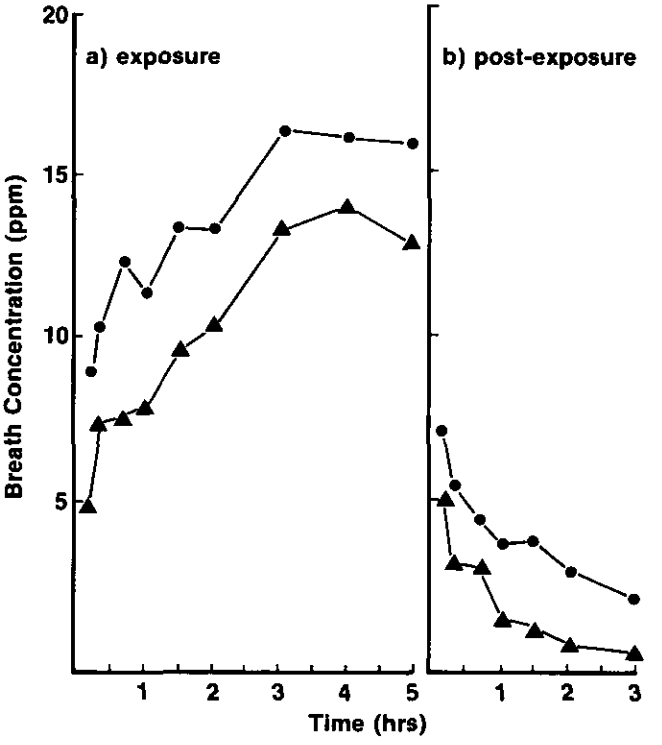

FIGURE 1. Exposure (*a*) and post-exposure (*b*) serial expired air concentrations of (▲) 2-propoxyethyl acetate and (●) 2-ethoxyethyl acetate in male beagle dogs. Exposure concentrations were 50 ppm for each compound. The results are expressed as the means from four dogs.

Table 1. Excretion of radioactivity by dogs following intravenous administration of [^{14}C]PEA or [^{14}C]EEA.[a]

	% of administered dose at various collection periods[b,c]			
	0–4 hr	4–8 hr	8–24 hr	Total (0–24 hr)
[^{14}C]PEA				
Urine	61.2 ± 2.9	17.3 ± 0.8	8.0 (7.7, 8.2)	88.6 (87.7, 89.4)
Carbon dioxide	0.8 ± 0.1	0.6 ± 0.1	[e]	[e]
Volatile organics	[d]	[d]	[e]	[e]
[^{14}C]EEA				
Urine	19.6 ± 7.0	18.6 ± 4.4	22.8 ± 2.5	61.1 ± 2.3
Carbon dioxide	0.7 ± 0.1	0.9 ± 0.1	[e]	[e]
Volatile organics	[d]	[d]	[e]	[e]

[a]Male beagle dogs were anesthetized for the 8-hr duration of the experiment. [^{14}C]PEA ([ethyl-1,2-^{14}C]2-propoxyethyl acetate) or [^{14}C]EEA ([ethyl-1,2-^{14}C]2-ethoxyethyl acetate) dissolved in saline (3 mL) was administered as a single dose of 1 mg/kg (10 μCi).
[b]Three dogs per group; mean ± SE except where only two values determined.
[c]Urine and expired air collected under anesthesia for 8 hr using a urinary catheter and endotracheal tube, respectively. Dogs were conscious and housed in metabolism cages for 8–24 hr urine collection.
[d]No radioactivity detected (or < 0.1% of dose).
[e]Not measured.

There was no GC evidence for the presence of volatile metabolites of either PEA or EEA in the expired air.

Intravenous Administration

After intravenous (IV) administration of [^{14}C]PEA (1 mg/kg), dogs eliminated about 88% of the radioactivity in the urine within 24 hr. The majority of this (61% of the dose) was eliminated in the first 4 hr (Table 1, Fig. 2).

After IV administration of [^{14}C]EEA (1 mg/kg) about 61% of the radioactivity was excreted in the urine within 24 hr. Only approximately 20% of the dose was eliminated in the first 4-hr period (Table 1, Fig. 2).

The blood concentrations of radioactivity (expressed as nmole equiv./mL) after IV administration of [^{14}C]PEA or [^{14}C]EEA are shown in Figure 3. A marked difference was observed between the blood clearance rates for PEA and EEA. After an initial, rapid distribution phase lasting approximately 30 min, the radioactivity from [^{14}C]EEA declined exponentially throughout the blood collection period, with an elimination half-life of 7.9 hr. The blood radioactivity after [^{14}C]PEA administration was cleared more rapidly. The elimination

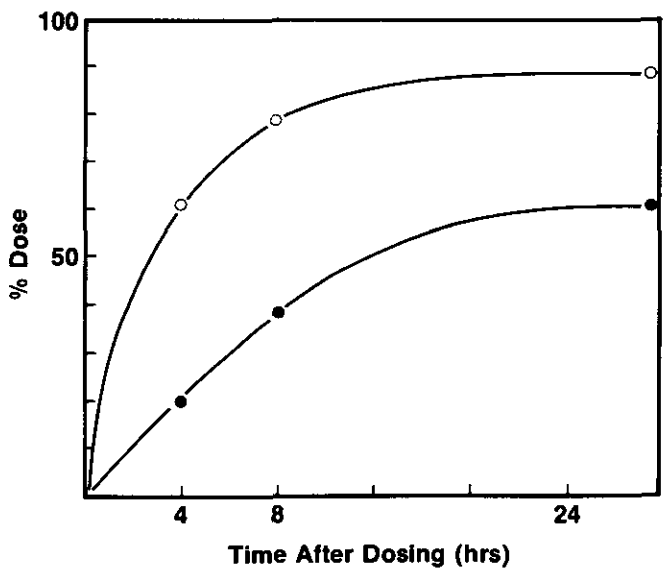

FIGURE 2. Urinary elimination of radioactivity in male beagle dogs following IV administration of (○) [ethyl-1,2-^{14}C]2-propoxyethyl acetate ([^{14}C]PEA) or (●) [ethyl-1,2-^{14}C]2-ethoxyethyl acetate ([^{14}C]EEA) (1 mg/kg). See Table 1 for experimental details.

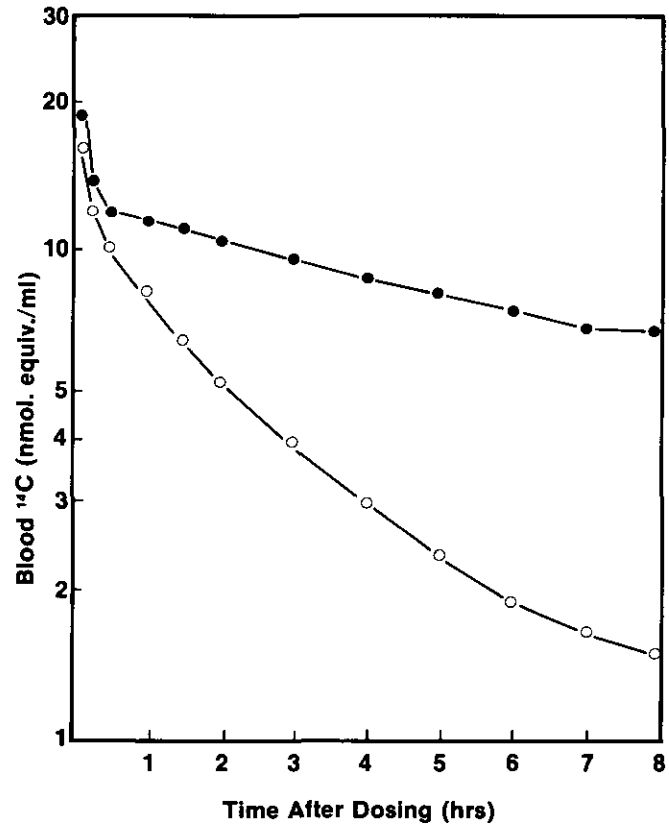

FIGURE 3. Blood concentrations of radioactivity in male beagle dogs following intravenous administration of (○) [ethyl-1,2-^{14}C]2-propoxyethyl acetate ([^{14}C]PEA) or (●) [ethyl-1,2-^{14}C]2-ethoxyethyl acetate ([^{14}C]EEA (1 mg/kg). Points represent the means of triplicate determinations in each of three dogs.

profile for [^{14}C]PEA was more complex and revealed a number of distinct phases with different half-lives. Estimation of the initial rate of elimination gave a half-life of 1.6 hr.

Small amounts of radioactivity (< 1% of the dose) were detected as $^{14}CO_2$ in the 4-hr and 8-hr collections from dogs receiving either [^{14}C]EEA or [^{14}C]PEA (Table 1). Trace amounts of radioactivity (< 0.1% of the dose) were expired as volatile organic materials from either [^{14}C]EEA or [^{14}C]PEA (Table 1).

Skin Exposure

The rates of percutaneous absorption and the elimination of radioactivity following 30-min or 60-min skin exposures to [^{14}C]EEA (110.5 mmoles) or [^{14}C]PEA (97.9 mmoles) are summarized in Table 2. Radioactivity was detected in the urine at 4, 8 and 24 hr after 30-min and 60-min exposures to both compounds (Table 2). After exposure to [^{14}C]PEA, urinary excretion of radioactivity was greatest at 4 hr and declined rapidly during the remaining collection period. After exposure to [^{14}C]EEA, urinary excretion of radioactivity was similar in the first two collection periods and was still substantial overnight (Table 2). These patterns of urinary ^{14}C excretion were similar to the respective excretion patterns seen after IV administration. No measurable concentrations of radioactivity were detected in the blood of dogs exposed for 60 min to [^{14}C]PEA or [^{14}C]EEA.

For each compound, the amounts absorbed were similar after 30-min and 60-min exposures (Table 2). Small amounts of $^{14}CO_2$ were detected in the expired air after exposure to both compounds.

In Vitro Percutaneous Absorption

The absorption of [^{14}C]PEA and [^{14}C]EEA through dog skin *in vitro* is shown in Figure 4. The lag times (time taken to reach steady state absorption) were calculated by extrapolation of the linear portion of each plot to the ordinate (Fig. 4, broken lines). The values obtained were 1.2 hr (PEA) and 1.6 hr (EEA). The slopes of the absorption plots indicate rates of absorption of 292 nmole/cm^2/min (2.3 mg/cm^2/hr) and 167 nmole/cm^2/min (1.5 mg/cm^2/hr) for EEA and PEA, respectively (Table 3). As judged by tritiated water permeability determinations (damage ratios) neither

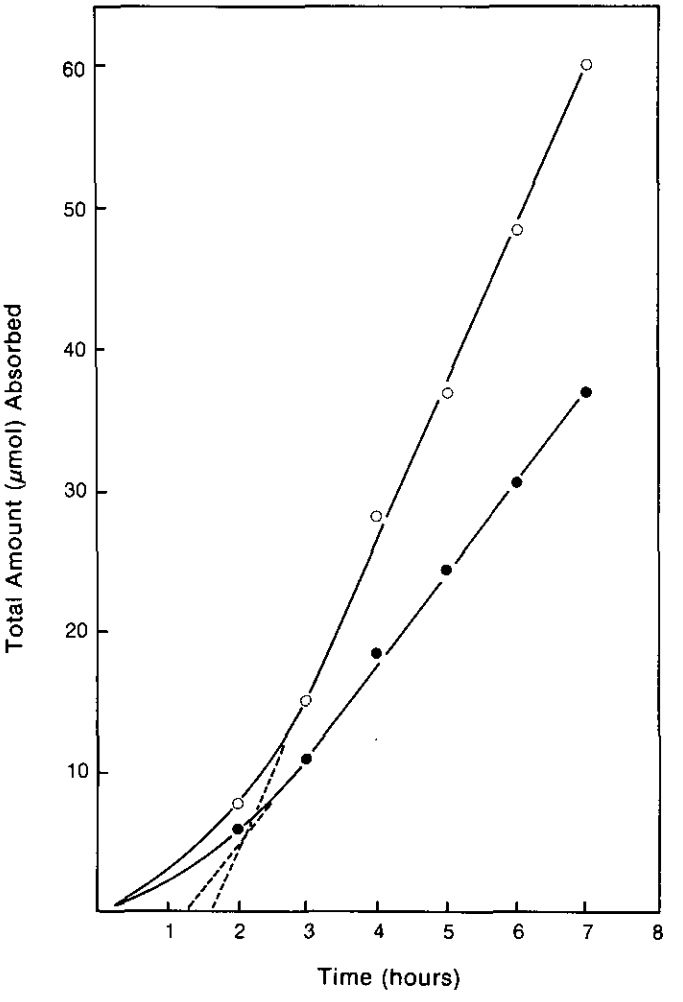

FIGURE 4. *In vitro* absorption of (●) 2-propoxyethyl acetate and (○) 2-ethoxyethyl acetate through skin from male beagle dogs. Points represent means of multiple determinations from each of two dogs.

Table 2. Percutaneous absorption and elimination in breath and urine of radioactivity by dogs exposed to [^{14}C]PEA or [^{14}C]JEEA.[a]

Compound	Exposure time, min	^{14}C in 8 hr breath, μmole/equiv.	Radioactivity in urine, μmole/equiv.[b]				Percutaneous absorption rate, nmole-cm^2/min[c]
			0–4 hr	4–8 hr	8–24 hr	Total	
[^{14}C]PEA	30	[d]	152.3 (179.7, 124.9)	71.4 (91.4, 51.4)	39.6 (59.9, 19.2)	263.3 (331.0, 195.5)	179.2
	60	5.7 ± 0.6	210.4 ± 16.7	84.4 ± 9.1	40.3 (52.5, 28.0)	343.9 (339.4, 348.3)	116.4
[^{14}C]EEA	30	[d]	60.2 (64.9, 55.5)	59.2 (63.5, 54.9)	105.7 (148.3, 63.1)	225.1 (276.1, 173.4)	219.3
	60	4.0 (5.8, 2.2)	62.5 ± 4.4	70.9 ± 15.6	91.7 ± 21.5	225.0 ± 40.8	109.6

[a][Ethyl-1,2-^{14}C]2-propoxyethyl acetate or [ethyl-1,2-^{14}C]2-ethoxyethyl acetate (15 mL) applied in 55.6 cm^2 skin absorption cell, approximately 40 μCi per experiment.

[b]Values presented are mean ± SE (where n = 3) or average (individual values) (where n = 2).

[c]Calculated after correcting for appropriate % excretion after IV administration (Table 1).

[d]Not collected.

Table 3. *In vitro* absorption of [^{14}C]PEA or [^{14}C]EEA through dog skin.

Compound	Absorption rate, nmole/cm^2/min[a]	Damage ratio[b]
PEA	163.0 ± 15.2	1.4 ± 0.2
EEA	279.7 ± 33.6	1.3 ± 0.1
Control[c]	—	1.4 ± 0.2

[a] $n = 9$.
[b] See methods for explanation ($n = 8$ or 9).
[c] Water applied to skin instead of glycol ether.

Table 4. Estimation of PEA or EEA uptake in man (from *in vivo* dog absorption studies).

Route of exposure	Exposure time, hr	Estimated uptake, mg	
		PEA	EEA
Inhalation (50 ppm)[a]	1.0	270	220
Skin (hands)[b]	0.5–1.0	580–760	640–645

[a] 1.25 m^3 inhaled per hr, absorption 74% (PEA) or 68% (EEA).
[b] 175 cm human, surface area 1.85 m^2; hands comprise 4% surface area.

EEA nor PEA altered the diffusion properties of the skin preparations (Table 3).

Discussion

The inhalation studies demonstrate that PEA and EEA are rapidly absorbed through the lungs. At equilibrium (about 3 hr) about 70% of the inhaled vapor was absorbed by the dogs. Both compounds appeared to be removed quickly from the blood, as indicated by the rapid decline in the post-exposure breath concentrations (Fig. 1). That the expired PEA concentrations were significantly lower than the EEA concentrations during the exposure may be a reflection of the more rapid blood clearance and urinary excretion rates for PEA (Tables 1 and 2; Figs. 2 and 3).

Blood concentrations of ^{14}C after IV administration showed different clearance rates for [^{14}C]PEA and [^{14}C]EEA, with elimination half-lives of 1.6 hr and 7.9 hr, respectively (Fig. 3). These differences were reflected in the urinary excretion rates, where ^{14}C from [^{14}C]PEA was excreted more rapidly than that from [^{14}C]EEA (Table 1 and Fig. 2). Similarly, after skin exposure, the urinary excretion rate for [^{14}C]PEA was greater than that for [^{14}C]EEA, even though the total amounts of each compound absorbed were comparable (Table 2).

The different elimination characteristics of PEA and EEA may result from differences in the metabolism of the compounds. At present, no data are available on the metabolism of PEA. Ethoxyacetic acid and *N*-ethoxyacetylglycine have been identified as metabolites of ethoxyethanol in rats after inhalation and oral administration. The combined excretion of the two metabolites was estimated to be 30% of the oral doses (*9*). Other ethylene glycol ethers, methoxyethanol, butoxyethanol and 2-(2-ethoxyethoxy)ethanol, have also been shown to be metabolized by oxidation to the corresponding alkoxyacetic acid (*10–12*). Dealkylation of [1-^{14}C-ethoxy]2-ethoxyethanol has also been reported (*13*). Thus it is reasonable to expect that PEA would undergo the same metabolic reactions as these related compounds. Different excretion rates for PEA and EEA may therefore reflect quantitative differences in metabolic products.

Although the excretion rates for PEA and EEA were markedly different, the total amount of each compound absorbed through the skin was similar (Table 2). The fact that, for each compound, approximately equal amounts of radioactivity were absorbed in 30 and 60 min may result from the relatively short exposure periods used in these experiments. Percutaneous absorption studies *in vitro* indicated absorption lag times of 1.2 hr (PEA) and 1.6 hr (EEA) with dog skin before steady-state absorption occurred, after which time EEA was absorbed at a faster rate than PEA (2.3 mg/cm^2/hr vs. 1.5 mg/cm^2/hr) (Fig. 4 and Table 3).

The data from the *in vivo* dog experiments may be used to estimate PEA or EEA uptake after human exposure, assuming that the rate of absorption in man is similar to that seen in dogs. Thus, after inhalation exposure for 1 hr at a concentration of 50 ppm, about 270 mg of PEA or 220 mg of EEA would be absorbed through the lungs. This is equivalent to about 2 g of material in an 8-hr day. After immersion of both hands for 30 to 60 min, about 580 to 750 mg of PEA or 640 mg of EEA would be absorbed through the skin. Extrapolating from the clearance rates in dogs, the absorbed PEA would be cleared more rapidly than EEA.

These absorption rates are similar to those obtained in our laboratory for other lipid-soluble chemicals, such as methyl *n*-butyl ketone and *n*-butanol (*14,15*).

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